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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 11/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/735,273	CLARK ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,17,19,29 and 36-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,14,17,19,29 and 36-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 7/7/03. Claims 12, 14, and 29 have been amended, claims 1-11, 13, 15, 16, 20-28, and 30-34 have been canceled, and claims 36-41 have been added. Claims 12, 14, 17, 19, 29, and 36-41 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is FINAL.**

2. Consonant with the previous species election (see paper filed 10/22/02) for claims which recite more than one gene the elected species fibronectin has been examined.

3. Claims 19, 37, 39, and 41 all refer to "the mammal," and while the claims to which they refer recite a human (which is a mammal) the claims would be more consistent and clearer if they referred to "the human" instead of the mammal.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 36 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claim 36 recites the limitation "the non-metastatic control" in line 8 of the claim. There is insufficient antecedent basis for this limitation in the claim as the claim previously recites a

metastatic control, not a non-metastatic control. Claim 37 depends from claim 36 and is rejected over this recitation as well.

7. Claims 12, 17, 19, 36, and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)."

In the instantly rejected claims, the new limitation of "excluding RhoC" in claims 12 and 36 appears to represent new matter. No specific basis for this limitation was identified in applicant's paper, nor did a review of the specification by the examiner find any basis for the limitation. Specifically, the exclusion proviso in which "RhoC" are distinguished is not found in the specification, to the contrary, the specification and claims as originally filed repeatedly refer to "RhoC" as a preferred embodiment of the claims. As noted by MPEP 2173.05(i),

> "Any negative limitation or exclusionary proviso must have basis in the original disclosure. See Ex parte Grasselli , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement."

Since no basis has been identified, the claims are rejected as incorporating new matter.

8. Claims 12, 14, 17, 19, 29, and 36-41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is reiterated in a modified form for claims 12, 14, 17, 19, and 29. The modifications to the rejection are to address the amendments to the claims. Further, the rejection is applied herein to newly added claims 36-41.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see In re Wands, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to:

a. Nature of the invention:

Claim 12 is drawn to a method of predicting the likelihood of development of a metastatic condition in a human, comprising the steps of (a) obtaining a biological sample from a human to be tested; (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the human; and (c) comparing the level determined in (b) with a non-metastatic control, wherein if the level determined in (b) is greater than the level of the gene product in the non-metastatic control, then the mammal has an increased likelihood of developing a metastatic condition. Claim 14 differs from claim 12 in that it recites a number of possible gene products, with fibronectin being the species of this listing elected for prosecution. Claim 17 depends from claim 12 and recites a number of possible metastatic forms. Claim 19

depends from claim 12 and recites that the biological sample is a blood sample or a cell sample from a tumor. Claim 29 specifically recites that the gene product is fibronectin.

Claims 36-41 differ from the preceding claims in that the control is a metastatic control, comparing step (c) states wherein if the level determined in (b) is the same as the level of the gene product in the metastatic control, then the mammal has an increased likelihood of developing a metastatic condition.

b. Breadth of the Claims: The claims as written are extremely broad, each for at least one of following reasons:

1) The claims read on predicting the likelihood of development of a metastatic condition. The claims do not recite the nature of the likelihood of development, how this increased or decreased likelihood is to be measured, or what constitutes a clinically or statistically significant change in the likelihood of developing a metastatic condition compared to a control. The claims read on a prediction made at any stage of the human's life, before the development of clinical samples, and potentially prior to birth if a sample is collected *in utero*. As broadly as written, the claims read on any prediction regarding development of a metastatic condition made at any point in the lifetime of a mammal. The claims encompass the prediction of the development of a metastatic condition in any type of cancer, for example.

3) The claims read on detection of any metastatic condition resulting from a neoplasm of any tissue in a human. Tumors arising from different tissues possess

significant differences in their progression, severity, and potential clinical outcomes.

4) The claims read on the testing of any biological sample. As broadly as written, the claims read on analysis of a tissue biopsy, blood sample, urine sample, or hair sample, for example.

5) The claims read on determining the level of any gene product or combination of gene products that alter the actin cytoskeleton. The claims do not specifically recite the nature of the alteration of the cytoskeleton, or the manner in which the gene product induces this alteration. Any change in cell shape or size requires an alteration of the cytoskeleton, as does movement of the cell, secretion of products by the cell, endocytosis, pinocytosis, exocytosis, cell division, apoptosis, and many types of transportation of substances from location to location within the cell. There is an large number of gene products which have the potential to either directly or indirectly affect any of these processes, and thereby alter the cytoskeleton.

As broadly as written, the claims read on the analysis of any of dozens of types of samples from humans, for the detection of any one of hundreds of gene products, or any combination thereof, for the purpose of determining any level of change in the likelihood of developing any of hundreds of metastatic conditions.

c. Amount of Direction and Guidance: The specification teaches the injection of two different melanoma cell lines (one mouse cell line (B16) and one human cell line (A375)) into mice (page 25). From metastatic lesions in these mice, cell lines were

developed which were identified as having increased metastatic potential relative to the parental cell lines. Differential display was carried out on these cell lines, and a number of differentially expessed genes were identified (Table 1, p. 19). Three genes, fibronectin, rhoC, and thymosin β4 were identified as being expressed at higer levels in all three metastases selected from both human and mouse samples (p. 30). The specification teaches numerous assays for proliferation, chemotaxis, and metastatic potential of the cell lines (page 28). The specification does not teach the collection or analysis of biological samples from other species of mammals, including humans, or from any species of mammal with a spontaneously-occurring metastatic condition.

d. State of the Prior Art / Level of Predictability in the Art: The prior art teaches numerous genes that demonstrate an altered level of expression in metastatic tissue. Suwa, et al., British Journal of Cancer 77(1):147-153, 1998 (hereinafter "Suwa"), for example, teaches a statistically significant correlation between expression of the rhoC gene in pancreatic ductal adenocarcinoma and metastasis. However, Suwa also teaches that no such correlation exists between metastasis and expression of genes closely related to rhoC such as rhoA or rhoB (Suwa, abstract).

With regard to claims which recite the measurement of fibronectin (FN) gene product as an indicator of metastatic potential, the prior art repeatedly teaches that the presence or increase of fibronectin expression and/or gene products in tumors is significantly associated with LOW metastatic potential (exactly the opposite result as implied by the instant amended and added claims). For example, Christensen *et al.* (Cancer Research, 48, 6227-6233, 1988) measured FN gene product via staining of the

FN protein itself in invasive breast carcinoma and found that while 87% of patients without evidence of metastatic spread had FN positive tumors, only 33% of women with metastatic spread had FN positive tumors (ABSTRACT and throughout). When they tested the metastatic lesions themselves, Christensen *et al.* found that the local recurrences tended to display the same staining pattern, whereas axillary lymph node metastases showed inconsistent staining patterns (p. 6228, paragraph bridging columns). Linlang *et al.* (Journal of Medical Colleges of PLA (1996), 11(3)224-226) teach that decrease or disappearance of FN in basement membrane plays a crucial role in tumor metastasis (p. 226). Xu *et al.* (Baiqiuen Yike Dixue Xuebao (1998) 24(4), 368-369, English abstract provided for applicant's convenience) teach that in the serum of non metastasis patients FN expression was more than double that of the expression in the blood of patients with metastasis lesions, and that the FN expression in the metastasized laryngeal tumor was faint or disappeared. Takei *et al.* (International Journal of Oncology, 12, 517-523, 1998) did not observe an association between FN expression and lymphnode metastases or tumor size in invasive breast carcinoma. These references highlight the extreme unpredictability associated with using an increased fibronectin expression observation in a tumor cell as an indicator of metastatic potential, since it has been shown that decreased FN expression in primary tumor is an indicator of increased metastatic potential, when there was an observable correlation. The instant specification shows only that FN expression is increased in metastatic lesions wherein these lesions originated from melanoma cell lines injected into mice. Cell lines may not be an accurate predictor of actual tumor progression, as these have been thorough multiple passages and

crises and have been being kept under artificial conditions. Thus, at best cell lines are a poorer representation of malignancy than the actual tumors examined in the prior art references cited herein because they have survived crisis and have adapted an immortal life in culture, and thus has been enabled to survive in its artificial environment.

e. Existence of Working Examples: The specification demonstrates that some genes are differentially expressed in metastatic lesions of cell lines injected into mice, and that in particular fibronectin is overexpressed in more highly metastatic cells. With regard to human cancers, a single cell line is examined. The specification does not test blood samples or primary tumor samples, or metastatic lesions that arise from actual primary tumors (as opposed to injected cell lines). The specification teaches the use of multiple cell lines of known metastatic potential injected into nude mice (page 25). The specification further teaches the creation of several sublines of A375 cells which overexpress rhoC, rhoA, or GFP (page 28). The specification teaches numerous assays for proliferation, chemotaxis, and metastatic potential of the cell lines (page 28) The specification does not teach the collection or analysis of biological samples from other species of mammals, or from any species of mammal with a spontaneously-occurring metastatic condition.

f. Quantity of Experimentation Required: The claims are drawn to the prediction of the likelihood of the development of a metastatic condition in a human based on an increased level of expression of a gene that alter the actin cytoskeleton, some claims particularly reciting fibronectin as the gene. In order to make and use the invention, one of skill in the art would be required to determine a particular metastatic condition and

species of human for further study. The skilled artisan would then be required to collect biological samples from normal individuals and those suspected of developing a metastatic condition. The level of expression of hundreds of genes would have to be determined, in triplicate to insure accurate results, from all tissue samples. The skilled artisan would then be required to wait, perhaps several years, to evaluate the progression of the metastatic conditions in the tested mammals using some form of objective and quantitative measuring system. If meaningful correlations between gene expression and the metastatic conditions can be derived, then the skill artisan can apply the assay to the specific condition assayed in the species of animal studied. In order to use the assay for any other condition, or in any other species of mammal, further validation of the assay will be required, which will entail several more years of study.

In view of the breadth of the claims, in view of the limited guidance provided by the specification, in view of the unpredictability of the art, in view of the level of experimentation required, the specification does not describe the claimed invention in such a way as to enable one of skill in the art to make and/or use the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The previous art rejections are withdrawn in view of applicant's amendments to the claims. New rejections are set forth to address the amended claims.

11. Claims 12, 17, 19, 36, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over van Gronigen *et al.* (cited in IDS, Cancer Research, 1995) in view of Steeg, et al., USPN 5,049,662, filed October 13, 1987, issued September 17, 1991 (hereinafter "Steeg").

Claim 12 is drawn to a method of predicting the likelihood of development of a metastatic condition in a human, comprising the steps of (a) obtaining a biological sample from a human to be tested; (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the human; and (c) comparing the level determined in (b) with a non-metastatic control, wherein if the level determined in (b) is greater than the level of the gene product in the non-metastatic control, then the mammal has an increased likelihood of developing a metastatic condition. Claim 17 depends from claim 12 and recites a number of possible metastatic forms, with melanoma being one of them. Claim 19 depends from claim 12 and recites that the biological sample is a blood sample or a cell sample

from a tumor. Claims 36 and 37 differ from the preceding claims in that the control is a metastatic control, comparing step (c) states wherein if the level determined in (b) is the same as the level of the gene product in the metastatic control, then the mammal has an increased likelihood of developing a metastatic condition.

Van Gronigen recites a method comprising the steps of: (a) obtaining a biological sample to be tested, wherein the biological sample is melanoma cell lines (page 6237, second column); (b) determining the level of lamanin gene product (clone 7) which is a gene products that alters the actin-based cytoskeleton of one or more tumor cells (page 6237, second column, "differential display"); and (c) comparing the level determined in (b) with an appropriate control (figure 2), wherein the controls include both metastatic and non-metastatic cells, and wherein there is an increased observation of lamanin gene expression in highly metastatic cells versus cells with non-metastatic (low metastatic) potential.

The teachings of van Gronigen determine the level of gene expression in a biological sample, and correlate the level of expression to the level of metastatic potential of cells. The teachings of van Gronigen are descriptive, however, and do not specifically teach that the method of van Gronigen could be applied to samples collected in the future in order to predict the likelihood of development of a metastatic condition in a mammal. However, the use of the descriptive teaching of Suwa as the basis for a predictive assay would have been obvious to those of ordinary skill in the art at the time the application was filed. Assays for the prediction of metastatic potential of tumor cells based on increased expression of specific genes were well known to those of ordinary skill in the art at the time the application was filed. Steeg, for example, teaches "an in vitro diagnostic kit for predicting the cancer metastatic potential of

tumor cells" (column 1, lines 27-30). In the assay taught by Steeg, "[h]ybridization of the cDNA clone for the NM23 gene to cellular RNA has predicted metastatic potential in both animal experimental metastasis model systems and human cancer" (column 5, lines 11-14).

Regarding claim 17, the metastatic form being examined by van Gronigen *et al.* is melanoma. Regarding claims 19 and 37, van Gronigen *et al.* exemplify the carrying out of the differential expression analysis in a comparison of cells from primary tumors, but do not complete this analysis for lamanin, or clone 7 as referred to therein. , Suwa teaches the embodiment in which the mammal is human (page 147, right column, third paragraph).

It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of van Gronigen *et al.* in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential. One of skill in the art would have been motivated to use a predictive assay based on Suwa because "[m]etastasis ... remains a primary cause of death for patients with solid tumors" (Steeg, column 1, 13-15).

Response to Remarks

The remarks are addressed as they are presented in turn beginning on page 6 of the response.

The amendment to the specification has been entered.

The amendments to the claims have been entered. New grounds of rejection are set forth to address the amended claims.

The 1449's have all been signed. Copies addressing the references that were not previously signed are enclosed with this office action.

The 112 1st paragraph rejection is maintained and modified to address the amended claims.

Applicants remind the examiner to consider the claim as a whole. The claims have been considered in their entirety, and the discussion of the parts of the claims is merely to demonstrate the breadth of the claims as written. The claims are extremely broad. For example, claims 12 and 36 encompass a predictive test that utilizes any gene whose expression product "alters the actin-based cytoskeleton," a genus of genes which is enormous considering all of the different mechanisms and processes which result in such alteration, as discussed in the rejection. Further, looking even at applicant's examples, the enormity of the genus encompassed by applicant's claims is evident as the genes characterized by applicant as "altering the actin-based cytoskeleton" are widely variant in their functioning.

Applicants point out that the scope of the claim has been narrowed for only prediction in humans, however this is not sufficient to overcome the rejection of record (newly applied) because applicant has not even demonstrated the functioning of their method in a human sample. One human cell line is used herein, and the metastatic cell lines used in the specification are derived from this cell line. No cell lines from primary human tumors or metastasis are examined to confirm the results observed in the mouse model using the cell line, and as cell lines may be a bad model for human cancer due to their altered status after crisis, for example, the results presented in the specification are not sufficient to support the claimed invention. Further, new arguments are set forth to address the amendments to the claims which require that an increased level of expression is indicative of the metastatic potential, especially with regard to fibronectin.

It is not at issue here whether one could perform differential expression assays, it is at issue whether these assays would be predictive in the ways that applicant's claims suggest. Quite simply, the specification has not provide sufficient evidence to support these claims, in light of the high level of unpredictability in this art, as is highlighted in the case of fibronecitn. The examiner is not requiring knowledge of any exact mechanism of action, but instead evidence of a clear association with predictive value, as is needed to practice the claimed invention.

The rejection discusses a number of factors that have led to the conclusion that undue experimentation would be required to practice the claimed invention, and for this reason, the rejections of record are maintained.

All previous art rejections are withdrawn in view of the amendments to the claims. New rejections are set forth to address the amended claims. It is noted that the teachings of van Groningen *et al.* provide only that lamanin is over-expressed in metastatic cell lines, and that the claims rejected under 103 are also rejected 112 1st paragraph herein, with the 112 1st paragraph lack of enablement rejection noting that cell lines may not be a good predictor of actual tumor activity. However, as the teachings of ban Groningen *et al.* provide at least as much as the examples in the specification (with regard to the fact that both show differential expression in tumor cell lines of varying metastatic potential), if the specification is shown to be enabling so will be the prior art, and in the interest of compact prosecution both rejections are set forth.

Conclusion

12. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Switzer
Examiner
Art Unit 1634

November 5, 2003

JEFFREY FREDMAN
PRIMARY EXAMINER